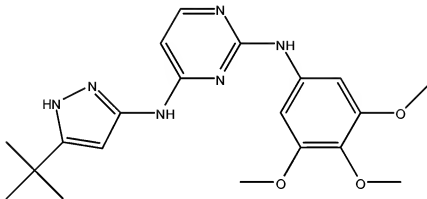


## REMARKS

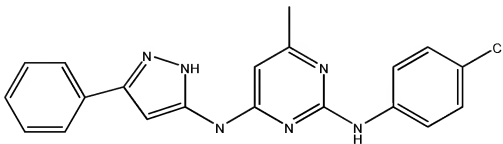
Claims 1-10, 14, 16-17, 20, 22 and 27 are pending in this application.

### Rejection under 35 U.S.C. § 103(a)

Previously, the Examiner has rejected claims 1-10, 14, 16-17, 20-22 and 27 under 35 U.S.C. § 103(a) as being unpatentable over International Publication No. WO 01/60816 A1 (hereinafter "Armistead") in the Office Action (hereinafter "Office Action") mailed on January 19, 2007. According to the Examiner, the skilled artisan in possession of the reference would have immediately recognized that a ring hydrogen could be replaced with another substituent such as a lower alkyl such as a methyl (CH<sub>3</sub>) substituent, without loss of the pharmaceutical activity. (*See* Continuation Sheet of the Advisory Action.) In support of his contention, the Examiner has pointed to compound 35 of Armistead (*see* page 28 of Armistead), where the pyrimidine ring is unsubstituted at the 5- and 6- positions, in support of his contention, as shown below (*see* page 5, first full paragraph, the Office Action):



According to the Examiner, the compound below, which is the eleventh compound in claim 8,



is representative of the claimed compounds, which “differ from the reference compounds by a -CH<sub>2</sub> group and are therefore, *structural homologs* of the reference compounds.” (See page 5, first full paragraph, the Office Action; and italics added.)

Applicants have filed an Amendment and Reply to the Office Action on July 19, 2007. In response to Applicants’ Amendment and Reply, the Examiner issued an Advisory Action (hereinafter “Advisory Action”) mailed on July 26, 2007, maintaining the obviousness rejection under 35 U.S.C. § 103 in view of Armistead. The Examiner further contended that Applicants are to provide a verified showing to establish the superiority of the claimed compounds that differed by a methyl group from the reference compounds. (See *id.*)

#### *Summary of Examiner Interview*

A telephonic interview between Examiner Deepak R. Rao and Applicants’ representative, H. Joon Chung, was conducted on January 23, 2008. In particular, the interview was directed to the rejection of the claims under 35 U.S.C. § 103(a) as being unpatentable over Armistead.

During the interview, Applicants’ representative explained that one of ordinary skill in the art would not have chosen compound 35 to modify in hope of making kinase inhibitors that fall within the scope of claims 1-10, 14, 16-17, 20-22 and 27 of the present application. Applicants’ representative directed the Examiner to Tables 2-4 on pages 69 and 70 of Armistead to indicate that contrary to the Examiner’s contention, one of ordinary skill in the art would not have chosen compound 35 but rather another compound that displayed better IC<sub>50</sub> results.

The parties agreed that Applicants’ representative would submit response to the pending Office Action and that the Examiner would consider the arguments of the response.

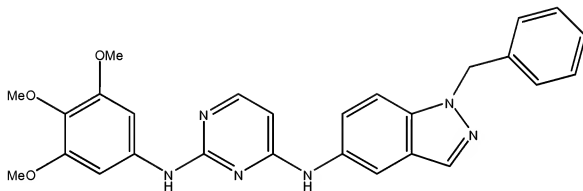
Applicants’ representative would like to thank Examiner Rao for his suggestion and time for advancing prosecution of the application.

#### *One skilled in the art would not choose compound 35 as a lead compound*

Rejecting claims 1-10, 14, 16-17, 20-22 and 27 of the present application under obviousness grounds, the Examiner contends that Armistead would have led one skilled in the art to select compound 35 to modify to arrive at compounds of the present application. Applicants, however, disagree with the Examiner’s reliance on compound 35 for the basis of the obviousness rejection. Elaborating the discussion during the Examiner interview, it is Applicants’ position that

one of ordinary skill in the art would not have chosen compound 35 out of sixty exemplified compounds (*see* Table 1, page 25 of Armistead) when Armistead provides more favorable compounds for inhibiting kinase.

To find compounds of claims 1-10, 14, 16-17, 20-22 and 27 obvious in view of Armistead, Armistead must have led one of ordinary skill in the art to select compound 35 as a lead compound. By “lead compound,” Applicants refer to a compound out of the sixty exemplified compounds that would be most promising to modify in order to improve upon its activity. However, compound 35 is not a lead compound. Tables 2-5 on pages 69-70 of Armistead indicate that compound 36 (shown below for convenience) has markedly better or equal IC<sub>50</sub> results than those of compound 35 in every enzyme category except one: in head-to-head comparison between the two compounds, compound 36 had better inhibiting activity in six enzymes (EGFR-1, ErbB2-1, Itk-1, KDR-2, PDGFRB and Zap-1) to compound 35’s one (Met-1).



In fact, when activities of compounds shown in Tables 2-5 of Armistead were compared in similar head-to-head fashion in the recited enzyme categories, there were, at least, two other compounds (compounds 31 and 37) that demonstrated better IC<sub>50</sub> results than compound 35. Excerpts from Tables 2-5 showing the head-to-comparisons of compounds 31, 35-37 IC<sub>50</sub> results are shown below for your convenience:

The tables herein utilize the following designations:

A < 1.5  $\mu$ M

B  $\geq$  1.5 and < 5.0  $\mu$ M

C  $\geq$  5.0 and < 10.0  $\mu$ M

D  $\geq$  10  $\mu$ M

ND = Not Determined

Excerpt from Table 2

Compound Number	Akt3-1	EGFR-1	ErbB2-1	ErbB4-1	FGFR1-1
35	D	C	D	C	C
31	D	D	ND	B	A
36	D	A	A	ND	ND
37	D	B	A	ND	ND

Excerpt from Table 3

Compound Number	Flt1-1	Fyn-1	Hck-1	IGFR-1	InsR-1
35	C	B	ND	A	A
31	A	A	D	ND	ND
36	ND	ND	ND	A	ND
37	ND	ND	ND	A	ND

Excerpt from Table 4

Compound Number	Itk-1	KDR-1	Lck-1	Lck-2	Lyn-1
35	B	B	A	A	A
31	B	A	A	A	A
36	A	A	A	A	ND
37	B	B	A	A	ND

Excerpt from Table 5

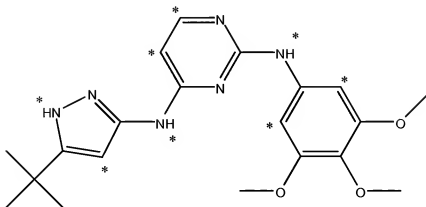
Compound Number	Met-1	PDGFRB	Ret-1	Src-1	Tek-1	Zap-1
35	A	B	B	A	ND	D
31	B	A	ND	A	C	D
36	B	A	ND	ND	ND	C
37	B	A	ND	ND	ND	D

Based on these results, Armistead would have led one of ordinary skill in the art to select compounds 31, 36 and 37 to modify, not compound 35, contrary to the Examiner's contention. And compounds 31, 36 and 37 are not structurally similar to any of compounds of claims 1-10, 14, 16-17, 20-22 and 27 to find them obvious because they all lack, for example, a pyrazole ring. Therefore, it is Applicants' position that the Examiner has not established prima facie obviousness of the claimed compounds in view of Armistead.

*No Prima Facie Obviousness - No teaching or motivation to modify*

Even if skilled practitioners would have chosen compound 35 to modify (which they would not) Armistead provides no motivation to modify compound 35 to arrive at Applicants' invention. As such, Applicants submit that the Examiner has failed to establish prima facie obviousness to sustain the rejection on this basis as well.

Armistead does not provide a reason for one of ordinary skill in the art to modify compound 35 to arrive at compounds of claims 1-10, 14, 16-17, 20-22 and 27. To render the compounds of the present application obvious based on the teachings of Armistead, one of ordinary skill in the art must: (1) choose compound 35 out of the *sixty exemplified compounds*; and (2) substitute hydrogen with a methyl group at one particular position out of *eight possible hydrogen positions on the rings and amines* (not including hydrogen positions on the substituted methyl groups).



\* indicates positions at which a methyl group can replace hydrogen

Nowhere does Armistead teach or disclose either of these two steps that are necessary for selecting and then modifying compound 35 to arrive at the compounds of the present application.

In order to find a *prima facie* case of obviousness in instances where close or established structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds, “a showing that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention [is] also required.” See *Takeda v. Alphapharm* (See Case No. 06-1329, 9 (Fed. Cir. decided on June 28, 2007; copy of the case is enclosed herein.; hereafter, “*Takeda*”), citing *In re Jones* (Fed. Cir. 1992); *In re Dillon* (Fed. Cir. 1990), *In re Grabiak* (Fed. Cir. 1985), and *In re Lalu* (Fed. Cir. 1984)). Importantly, the court in *Takeda* further stated that “[t]hat test for *prima facie* obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.” (See *id.*)

The findings of *Takeda* relate to the instant circumstance because both situations involve “walking” of substituents. More specifically, *Takeda* relates to the instant circumstance because: (i) in order to compare the compounds of the present invention to Armistead, prior to determining to substitute one of the ring or amine hydrogens, one skilled in the art must “walk” the methyl group on the eight possible positions on a pyrimidine ring, a pyrazole ring and two amines; and (ii) *Takeda* involved homologation and methyl walking in the transformation of a prior art compound to the compared compound of the present application.

“[I]n cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a *particular manner* to establish *prima facie* obviousness of a new claimed compound” (emphasis added). See *Takeda*. Nothing in Armistead provides the reason or motivation to modify compound 35 in the particular manner required to transform it into one of the claimed compounds of the present application. Accordingly, Applicants respectfully request that the obviousness rejection of claims 1-10, 14, 16-17, 20-22 and 27 be withdrawn.

#### Information Disclosure Statement

An Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the IDS is respectfully requested.

### CONCLUSION

In view of the above remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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